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The role of vitamin D/VDR signaling within key mechanisms of ulcerative colitis

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Statement of the Problem: Epidemiological evidence has shown an associative relationship between low serum vitamin D levels (<35 ng/mL) and disease activity in ulcerative colitis patients. The biological activity of vitamin D is observed to occur through ligand bonding with the VDR, which is highly expression within intestinal epithelial cells. Due to the observed immune modulatory effect of vitamin D/VDR signaling and the high expression of the VDR within the intestinal track, this review aims to elucidate what role vitamin D/VDR signaling may play in key mechanisms of colitis is to include intestinal barrier dysfunction, IEC apoptosis, macrophage inflammation, reduced and penetrable mucus layer. Furthermore, due to the associative link between low serum vitamin D and disease, this review aims to critically appraise the efficacy and safety of vitamin D supplementation in UC patients.

Methodology: A systematic and replicable search strategy was employed within this review. PubMed was systematically search from 2005 to 2016 using the terms ulcerative colitis or colitis or inflammatory bowel disease or IBD, followed by key search terms pertinent to the mechanism under investigation. Of the 1140 papers returned, 80 papers were accepted within this review.

Results: Within this review, TNF-a was observed to promote intestinal permeability, macrophage inflammation and apoptosis in a NF-kB dependent mechanism. TNF-a signaling was observed to up regulate the expression of the NF-kB protein p65, which was observed to promote intestinal permeability through the up regulation and phosphorylation of myosin light chain kinase, to promote intestinal epithelial cell apoptosis through the up regulation of p⁵³ Up regulated Modulator of Apoptosis (PUMA) and to promote excessive and prolonged macrophage inflammation through the inhibition of Suppressor of Cytokine Signaling 1 (SOCS1). Conversely, vitamin D/VDR signaling emerged as a key inhibitor of P⁶⁵ associated transcriptions, being observed to physically bind with the p65 protein and attenuate its transcriptional activity. The VDR was observed to be significantly down regulated in the active lesions of ulcerative colitis patients and significantly associated with an exacerbation of colitis symptoms in murine models. TNF-a was observed to actively down regulate the expression of the VDR in a microRNA-346 dependent mechanism, whereas, 1, 25(OH) 2D3 supplementation was observed to promote VDR expression. An associative relationship was proposed within this review between vitamin D/VDR signaling, cathelicidin expression and the promotion of mucus production. However, there was paucity in studies investigating this relationship explicitly and so the association remains speculative at this time. 1, 25(OH) 2D3 supplementation emerged as a safe and effective way to increase serum vitamin D levels in ulcerative colitis patient, with 2000 IU/day being observed as an efficacious, safe dose associated with increased serum vitamin D levels.

Conclusion & Significance: Increasing mechanistic evidence suggests a role for vitamin D/VDR signaling within key mechanisms of colitis. Further investigation is required to ascertain whether VDR down regulation in the active lesions of UC patients is an associative factor in colitis severity and progression. The therapeutic potential of vitamin D supplementation in ulcerative colitis patients' warrants further investigation in long term randomized controlled trials.

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